REMARKS

Claims 1-3, 5-7, 18-24, 26-30, 32-36, 38 and 39 are pending in the present Application. Claims 4, 8-17, 25, 31, 37 and 40-43 have been withdrawn from consideration, Claims 1, 23 and 29 have been amended, and Claims 44 and 45 have been added, leaving Claims 1-3, 5-7, 18-24, 26-30, 32-36, 38, 39, 44 and 45 for consideration upon entry of the present Amendment. The Specification has been amended to correct certain typographical errors.

Claims 1, 23 and 29 and paragraphs 5 and 55 have been amended to correct a typographical error in the formula for the prenyl isoflavonoids. Support can be found in the formula itself.

Claims 1, 23 and 29 have been amended to replace "and" with "or" to clarify, for example, that only one wogonin, ester, salt, or selectively substituted analog is required.

Support for new claims 44 and 45 can be found in the Specification as filed in paragraph [00119].

No new matter has been introduced by these amendments claims. Reconsideration and allowance of the claims are respectfully requested in view of the above amendments and the following remarks.

Interview Summary

Applicant thanks the Examiner for the telephonic interview with Karen A. LeCuyer on 10/3/2006. The Ogasawara et al. reference and the Examiner's calculations were discussed. The Applicant was encouraged to explain that in vitro data does not correlate to the therapeutic dosage amount. The Examiner did caution that he may search the non-elected species after receipt of this response.

Information Disclosure Statement

Applicants note that the Examiner has not considered the art submitted in the Information Disclosure Statements filed: 12/09/2005, 09/30/2004, 04/08/2004, 02/05/2004, 11/12/2003, and 11/03/2003. Applicants respectfully request that the art submitted in these Information Disclosure Statements be considered and a fully initialed PTO Form A820 be returned to the Applicants.

Claim Objections

Claim 29 is objected to because of the following informalities: Claim 29 ends with two periods. Claim 29 has been amended accordingly. Withdrawal of the claim objection is respectfully requested.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-3, 5-7, 18-24, 26-30, 32-36 and 38-39 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner alleges it is unclear what active agents and/or how many active agents are required to meet the claim limitations.

Claims 1, 23 and 29 have been amended to replace "and" with "or" to clarify, for example, that only one wogonin, ester, salt, or selectively substituted analog is required. Only one phytoestrogen is required in the claimed composition. For example, when the phytoestrogen is a wogonin, it is "wogonin, its pharmaceutically acceptable esters and salts, or its selectively substituted analogs represented by formula (1)".

Reconsideration and withdrawal of this rejection are respectfully requested.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 1-3, 5-7, 18-24, 26-30, 32-36 and 38-39 stand rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over Ogasawara, et al. "Screening of Natural Compounds for Inhibitory Activity on Colon Cancer Cell Migration"; Biol. Pharm. Bull.; 24; pp 720-723; (2001), in view of Yamamoto, et al. "The Potent Anti-Tumor-Promoting Agent Isoliquiritigenin"; Carcinogenesis; 12; pp 317-323; (1991). Applicants respectfully traverse this rejection.

Ogasawara et al. is directed to screening of natural compounds for inhibitory activity on colon cancer cell migration. Wogonin is listed as one compound that inhibits tumor cell migration in vitro with an IC_{50} of 86.9 μg/ml for migration and 26.3 μg/ml for proliferation. (Table 2)

Yamamoto is directed to a study of the anti-tumor activity of isoliquiritigenin. (Abstract)

In making the rejection, the Examiner states that Ogasawara et al. "teach the IC50 of wogonin to be 86.9 μg/ml which is calculated to be a ratio of 15.7 to 1in one ml of water (MW of water is 18 g/ml and the MW of wogonin is 284 g/mol giving a 15.7 to 1 ratio) and therefore suggests the efficacy of a composition comprising greater than 0.5 weight percent of wogonin". (September 8, 2006 office action, pp. 3-4) The Examiner then states "Ogawawara et al. do not teach combination therapies of a particular amount of wogonin to a human." (September 8, 2006 office action, p. 4) The Examiner relies on the teaching of Yamamoto et al. that isoliquiritigenin has antitumor properties, stating "combining agents which are known to be useful as chemotherapeutics individually into a single composition useful for the very same purpose is prima facie obvious". *Id.*

For an obviousness rejection to be proper, the Examiner must meet the burden of establishing a prima facie case of obviousness. *In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Establishing a prima facie case of obviousness requires that all elements of the invention be disclosed in the prior art. *In Re Wilson*, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

The present claims are directed to compositions comprising greater than 0.5 weight percent of a phytoestrogen based on the total weight of the composition and methods of using the compositions. Applicant respectfully submits that the cited art does not teach or suggest this particular claim element.

Ogasawara et al. lists wogonin as a compound that inhibits tumor cell migration in vitro with an IC_{50} of 86.9 μg/ml for migration and 26.3 μg/ml for proliferation. (Table 2) The Examiner then takes the 86.9 μg/ml and calculates a ratio of 15.7 to 1 in one ml of water (MW of water is 18 g/ml and the MW of wogonin is 284 g/mol giving a 15.7 to 1 ratio). Applicant is puzzled by the Examiner's calculation and the relevance thereof. First, the 86.9 μg/ml refers to μg of wogonin per ml of water. The molecular weights of wogonin and water are irrelevant. If one wanted to convert the 86.9 μg/ml to a weight percent, one would take the density of water which is roughly 1g per ml and then convert 86.9 μg/ml to 86.9 g wogonin in 1 g water or 0.00869 wt%. This is very far below the presently claimed wt% of greater than 0.5 wt%. Thus, Ogasawara et al. does not teach a composition having the claimed wogonin concentration.

More fundamentally, the therapeutic dosage of a drug for use in humans cannot be determined based on the in vitro data, particularly in vitro data of one particular type of cancer cells. There are two basic elements required for the establishment of drug dosage, namely safety and efficacy. The in vitro data in call lines does not correlate to a therapeutic dosage. The dosage range claimed in the present application was based on the response data of prostate cancer patients (i.e., human data) who failed conventional therapy including an androgen ablation drug, flutamide, and surgery. It is this type of human data that is required to determine the therapeutic dose for humans and that is missing from the references cited by the Examiner.

For example, in an abstract of an article by Boxenbaum and DiLea it is clearly stated that there are many factors in dose selection for humans including "animal toxicology, toxicokinetics, allometric scaling, pharmacokinetics, body surface area correlations, and integration of preclinical pharmacologic and toxicologic data". (Attachment A) Kouno et al. emphasizes the importance of selecting the proper dose of ant-cancer agents. (Attachment B, Abstract) Body surface area is described as one method to calculate the dose of anticancer therapy. *Id.* Thus, one cannot merely extrapolate from an in vitro cell culture experiment to a suitable human therapeutic dose. One needs to take into account many factors such as the pharmacokinetics and pharmacodynamics. Thus, an cell culture experiment such as that in Ogasawara et al. does not address the therapeutic dose of an anti-cancer agent.

Yamamoto et al. does not cure the defects of Ogasawara et al. Like Ogasawara et al. Yamamto et al. presents only in vitro and not in vivo human data. Thus, Yamamoto et al. does not disclose therapeutic amounts of any compound.

For at least the foregoing reasons, Applicant submits that the references cited by the Examiner fail to teach at least one element of the present claims, the claimed concentration of phytoestrogen. Thus, these references do not render the present invention obvious.

Reconsideration and withdrawal of this rejection are respectfully requested.

It is believed that the foregoing amendments and remarks fully comply with the Office Action and that the claims herein should now be allowable to Applicants. Accordingly, reconsideration and withdrawal of the objection(s) and rejection(s) and allowance of the case are respectfully requested.

If there are any additional charges with respect to this Amendment or otherwise, please charge them to Deposit Account No. 06-1130.

Respectfully submitted,

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ATTACHMENT A

The Journal of Clinical Pharmacology, 1995; 35:957-966

Articles

First-time-in-human dose selection: allometric thoughts and perspectives

H Boxenbaum and C DiLea

Some of the many factors that influence dose selection in first-time-in-human studies are examined. These include animal toxicology, toxicokinetics, allometric scaling, pharmacokinetics, body surface area correlations, and integration of preclinical pharmacologic and toxicologic data. Appropriate preclinical evaluation and analysis may reduce the frequency and severity of unexpected toxic events arising during single-dose, phase I testing. However, significant intrinsic uncertainties in this process presently exist and will continue to exist well into the foreseeable future. With our present state of knowledge, we cannot provide a realistic and reasonable algorithm for ascertaining first-time-in-human doses: any decision tree would be too unwieldy. There are several rules of thumb that do have a place in the evaluation and decision-making process, however.

ATTACHMENT B

Jpn J Clin Oncol 2003;33(6)309–313

Standardization of the Body Surface Area (BSA) Formula to Calculate the Dose of Anticancer Agents in Japan

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Received January 19, 2003; accepted May 28, 2003

Background: The importance of deciding the appropriate dose of anticancer agents cannot be overemphasized. Body surface area (BSA) has been used to calculate the dose in anticancer therapy since the 1950s. Japanese oncologists, often use their own Japanese BSA formula instead of western BSA formulae. However, it is not widely known that some discrepancies exist between the BSA products of the Japanese and western styles. On the other hand, recently dose-calculations according to BSA were criticized from the standpoint of pharmacokinetics (PK). Lately, we have had many opportunities for international collaborations, which make it necessary to review these BSA formulae, and the BSA-based dosing method. A unified BSA formula in cancer therapy is needed in Japan.

Methods: We searched and compiled frequently used BSA formulae across the world using the MEDLINE search, oncology text, a web search on cancer clinical trial groups, and personally communicated with medical oncologists from western countries. Using these formulae, we calculated BSA for a typical Japanese individual, and compared their products. We calculated BSA using these formulae for individuals of widely varying physique, from 140 to 185 cm in height, and from 30 to 96 kg in weight, and estimated the amount of discrepancies among them.

Results: Among the various BSA formulae used in western countries, the DuBois formula is the standard. In Japan, the Fujimoto formula has been used frequently. The Fujimoto formula was based on a study of 201 Japanese subjects in 1949. For the average Japanese individual, the BSA calculated using the Fujimoto formula was about 3% lower than that which was calculated by western formulae. The BSA calculated for all heights and body weights using the Fujimoto formula, ranged between 0.7 and 4.8% less than those calculated by using the DuBois formula. The other western formulae showed larger discrepancies than the Fujimoto and DuBois formulae.

Conclusion: BSA-based dosing has failed to standardize the variation in PK for most anticancer agents, and individual dosing techniques are currently being investigated. However, until their clinical utilities are confirmed, it is necessary to depend on the BSA-based calculation for determining the dose of most anticancer agents. The DuBois formula, which is the western standard formula, is validated to a greater extent and its accuracy has been confirmed more than others, including the Fujimoto formula. We recommend the use of the DuBois formula instead of the Fujimoto formula in cancer chemotherapy and propose the standardization of this formula in Japan.

Key words: body surface area – dose – calculation – pharmacokinetics – anticancer agents

INTRODUCTION

It is very important to determine the appropriate dose of anticancer agents. Individuals have varying abilities to metabolize and eliminate drugs, and therefore the same dose of anticancer agents will have different pharmacokinetics (PK) and pharmacodynamics (PD). In addition, there is a presumed narrow therapeutic index for most anticancer agents. Reducing the dose of these agents not only reduces toxicity but also the effects on the tumor. This has been shown in breast cancer (1,2), testicular cancer (3), lymphoma (4), and other cancers. It is necessary to balance the ability of the normal tissue to withstand insult and the intrinsic sensitivity of the tumor. Selecting doses of anticancer agents to treat cancer patients can be a challenging decision for medical oncologists.

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Table 1. Search results on the BSA formulae

Author	Year of publication	No. of Patients	Formula
DuBois and DuBois (7)	1916	9	$BSA = 0.007184 \times H^{0.725} \times W^{0.425}$
Boyd	1935	411	$BSA = 0.017827 \times H^{0.5} \times W^{0.4858}$
Gehan and George (9)	1970	401	$BSA = 0.0235 \times H^{0.42246} \times W^{0.51456}$
Haycock et al. (10)	1978	81	$BSA = 0.02465 \times H^{0.39646} \times W^{0.5378}$
Mosteller (11)	1987	*	$BSA = \sqrt{H \times W/3600}$
Takahira (5)	1925	Unknown	$BSA = 0.007241 \times H^{0.725} \times W^{0.425}$
Fujimoto (5)	1968	201	$BSA = 0.008883 \times H^{0.663} \times W^{0.444}$

*Conducted by modifying the Gehan and George formula.

In cancer chemotherapy, the doses of chemotherapeutic agents are generally calculated using the body surface area (BSA). Various studies have estimated BSA, and currently several BSA formulae are being used across the world. In Japan, the Fujimoto BSA formula (5), is often used to calculate the dose of anticancer agents in practice or in clinical trials. The Fujimoto formula was first reported approximately forty years ago, and has been subject to the criticism that it may not be suitable for modern Japanese people. Recently, we have had several opportunities for international collaborations and thus we need to standardize the BSA formula. Therefore, we reviewed the BSA formulae and BSA-based anticancer agent dosing, and examined the validity of the Japanese BSA formula.

METHODS

We searched and compiled the frequently used BSA formulae across the world using the MEDLINE search, oncology text, a web search on cancer clinical trial groups, and personally communicated with medical oncologists from western countries. Using these formulae we calculated BSA for a typical Japanese individual, and compared their products. We performed calculations using these formulae for individuals of widely varying physique ranging from 140 to 185 cm in height, and from 30 to 96 kg in weight, and estimated the amount of discrepancies among them.

RESULTS

There were two method groups calculating BSA. The first group utilized both body height and weight. These had the same functional form, that is, $BSA = a0 \times H^{a1} \times W^{a2}$, with different coefficient values. The BSA calculations of the second group did not utilize the preceding formula, and chiefly utilized only body weight. The latter formulae have not been utilized in calculating the dose of anticancer agents because of their inaccuracy (6). Our search results showed seven representative BSA formulae of the former type (Table 1). Among them, the DuBois and DuBois (7), Boyd (8), Gehan and George (GG) (9), Haycock, Schwarta and Wistosky (10) and Mosteller (11) formulae were from western countries, while the Takahira and Fujimoto formulae (5) were from Japan. Among the clinical trial groups, for example, the Southwest Oncology Group (SWOG), described in its policy that the BSA can be determined from weight and height using a nomogram found in standard references (12). The DuBois formula has been used as the standard formula in western countries (13). The Cancer Therapy Evaluation Program (CTEP) in the United States of America has decided not to recommend any particular formula to be used for BSA-based dose calculation in NCI-sponsored treatment trials (12). The Gynecology Oncology Group's (GOG) statistical and data center has adopted western formulae such as the DuBois, Mosteller, Gehan, and Haycock formulae (14), whereas the Japan Clinical Oncology Group (JCOG) has adopted the Japanese Fujimoto formula (15).

For example, in the case of a patient whose height was 170 cm and body mass index was 22 kg/m^2, the BSA calculations using the western formulae and the Takahira formula resulted in similar products, that is, ranging between 1.73–1.75 m^2 (the DuBois formula was at 1.74 m^2). However, for the same example, the BSA calculated using the Fujimoto formula was 1.69 m^2, which was about 3% lower than the others.

Figure 1 graphically displays the discrepancies between the respective formulae and the Fujimoto formula, which is frequently utilized in Japan. Compared to the Fujimoto formula, the Boyd, GG, Haycock and Mosteller formulae have a tendency to overestimate the BSA of short and obese patients and to underestimate it for tall and thin patients. Among these examples, the maximal overestimation was 0.2 m^2 by the GG formula and the maximal underestimation was 0.096 m^2 by the Haycock formula. The discrepancies between the DuBois and Fujimoto formulae ranged between 0.013 m^2 (0.9%) in the shortest and most obese patient (140 cm, 96 kg) and 0.061 m^2 (4.7%) in the tallest and thinnest patient (185 cm, 30 kg). This discrepancy between the DuBois and Fujimoto formulae was smaller than the discrepancies between other western formulae and the Fujimoto formula.

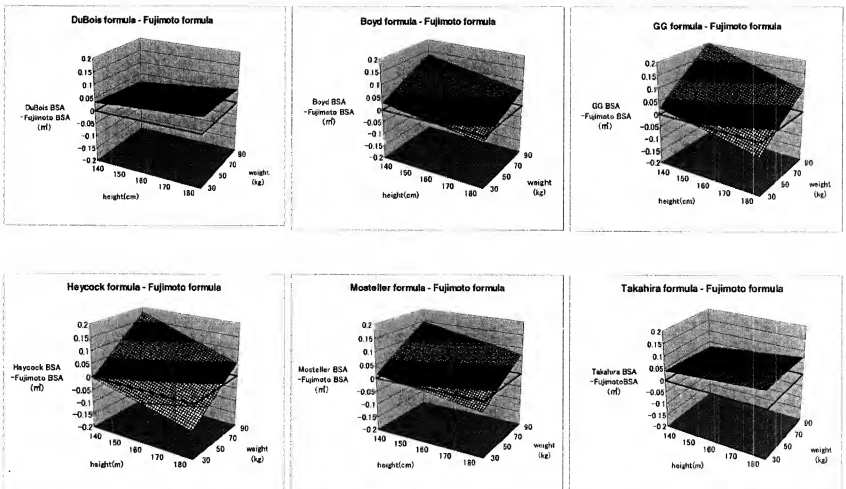

Figure 1. The discrepancies among respective formulae and the Fujimoto formula. The Boyd, GG, Heycock and Mosteller formulae tend to overestimate the BSA of short and obese patients and to underestimate the BSA of tall and thin patients compared to the Fujimoto formula. The discrepancies between the DuBois and Fujimoto formulae range between 0.013 m^2 (0.9%) in the shortest and most obese patient (140 cm, 96 kg) and 0.61 m^2 (4.7%) in the tallest and thinnest patient (185 cm, 30 kg). These discrepancies are smaller than the discrepancies among the other western formulae and the Fujimoto formula.

DISCUSSION

In 1916, DuBois and DuBois reported the BSA formula with direct measurements of nine subjects including a 36-year-old cretin, with an underdeveloped physique, a 12-year-old boy, a tall, thin adult male, and a short, obese adult female (7). In 1935, Boyd reported a formula as a result of investigating 411 subjects (8). In 1970, Gehan and George reported another formula based on the study of 401 subjects (9), and in 1978, Haycock, Schwarta and Wistosky reported another formula based on the measurements of 81 Caucasian, African American and Hispanic subjects (10). In 1984, Martin et al. determined the BSA from 20 aged cadaver subjects by planimetry on paper tracings of dissected skin and compared the measured surface area with the BSA predicted by the DuBois formula. They concluded that the predicted BSA did not differ significantly from the measured surface area and recommended continued use of the DuBois formula (16). In 1987, Mosteller modified the GG formula and simplified it to enable calculation using a pocket calculator (11). This formula has become popular because it is easy to use. In 1992, Wang et al. attempted to determine the accuracy of the BSA formulae proposed in these studies and examined their applicability to patient populations such as neonates and parturients (6). They directly measured the surface area with 60 pregnant women (34 to 40 week gestation) and 148 neonates. Regardless of these highly varying statures, the DuBois formula and other western formulae adequately predicted the measured surface area and they finally recommended the DuBois formula as a standard formula. However, their study did not include the Japanese formulae described below.

In Japan, Takahira et al. (in Fujimoto et al., Ref. 5) considered the DuBois formula inappropriate for Japanese individuals and constructed a new formula based on predetermined conditions, in 1925. In 1968, Fujimoto et al. (5) reported their formula with the direct measurement of 201 subjects, dividing them into three major age groups, namely, infants, children and adults. The Fujimoto formula for adults is one of the most commonly used formulae to calculate the dose of anticancer agents in Japan.

For a typical case where the height was 170 cm and the body mass index was 22 kg/m^2, the five western formulae and the Takahira formula calculations resulted in similar BSA products. However, compared with the other formulae, only the Fujimoto formula underestimated BSA by about 3%. Therefore, it was suggested that the anticancer agents might be underdosed in Japanese patients when using the Fujimoto formula.

BSA was calculated for individuals of widely varying physique from 140 to 185 cm in height, and from 30 to 96 kg in weight. The amount of discrepancies among these formulae was estimated. Since Japanese oncologists frequently use the Fujimoto formula, we evaluated the discrepancies between the Fujimoto formula and the six other formulae. Compared to the Fujimoto formula, the Boyd, GG, Haycock and Mosteller formulae have a tendency to overestimate the BSA of short and obese patients and to underestimate it for tall and thin patients. The discrepancy between the Fujimoto and DuBois formulae was relatively smaller than the discrepancies between the Fujimoto formula and other western formulae.

At present, dose calculations of most anticancer agents are made using BSA. BSA-based cancer chemotherapy began about a half century ago. In 1958, Pinkel (17,18) examined previous studies and determined the conventional pediatric and adult doses for five cytotoxic agents (Mercaptopurine, Methotrexate, Mechlorethamine, Triethylenethiophosphomide, and Actinomycin). For the same drugs, the appropriate therapeutic dose, for experimental animals was also determined from literature. These doses, per unit BSA, were calculated using a representative BSA, estimated using the DuBois formula for humans (7), and for the Meeh's formula for animals (5), which were then compared. It was found that similar values for the doses per unit surface area were obtained for each agent. Then, the use of BSA was recommended for performing dose calculations in chemotherapy. Since the publication of this report, the use of BSA for dose calculations of cytotoxic chemotherapy has become a standard practice.

However, this BSA-based dose calculation was recently criticized (19–22) because it failed to standardize the interpatient variation in PK. PK was analyzed in etoposide (23), calboplatin (24), epirubicin (25), paclitaxel (20), cisplatin (26), CMF (cyclophosmamide, methoterexate, and 5-fluorouracil) (27) and the other anticancer agents or combinations thereof and showed significant interpatient variability regardless of BSA-based dose calculations. With regards to cisplatin, Felix reported a mean plasma clearance of unbounded cisplatin with an interpatient variability of 25.6% (in Moore et al., Ref. 26) and showed that BSA-based dosing did not decrease the variability of unbounded cisplatin clearance. However, Bruno et al. (in Calvert et al., Ref. 28) showed that the variation of docetaxel clearance correlated with BSA. On the whole, most investigators reported that BSA did not correlate with the PK of most anticancer agents.

Besides the BSA-based calculations, several other individual dosing techniques have also been investigated. Calvert et al. (28) showed that the glomerular filtration rate (GFR) alone can predict area under the curve (AUC) for calboplatin, independent of BSA. The dose-calculation formula using patients' GFR was devised to predict AUC for calboplatin. Yamamoto et al. (29) reported that docetaxel clearance did not correlate to BSA and showed that it could be predicted by measuring 6-β-hydroxycortisol after cortisol administration. The possibility of a decrease in the variability of PK and PD by individual dosing of docetaxel is currently being investigated in a prospective trial. However, the complexity of metabolism and elimination of most other cytotoxic drugs makes the deviation of simple formulae difficult, and definitive evidence is awaited.

Therapeutic drug monitoring (TDM) and pharmacological adaptive control has been investigated for some anticancer agents. Methotrexate was one such example. Evans et al. (30) showed, in a prospective trial, that adjusting the dose of methotrexate with TDM to account for the patient's ability to clear

the drug could decrease the variability of PK and moreover, it could improve continuous complete remission in children with B-lineage acute lymphoblastic leukemia. However, TDM can be utilized in the second or later course of chemotherapy because the PK data of the previous course is necessary. Therefore, this technique cannot be used to determine the initial dose, unless a test dose is administered. Further, the introduction of TDM into clinical practice would be difficult because of its cost and inconvenience. Until these problems are overcome or individual dosing techniques are developed, we have to depend on the BSA-based dose calculations for most anticancer agents.

To summarize, the Fujimoto formula is frequently used in Japan. Though this formula was proposed over forty years ago, with the study of 206 Japanese patients, no recent studies have supported the validity of this formula, especially with regard to the modern Japanese physique which has become similar to that of people in western countries. The Takahira formula is not popular and has not been validated. As mentioned above, the results of the Boyd, GG and Haycock formulae showed larger discrepancies as compared with the Fujimoto and DuBois formulae. The DuBois formula has been a standard formula in western countries. Several studies have validated the accuracy of this formula (6,16,19). There was a relatively small discrepancy between the Fujimoto and DuBois formulae. However, the possibility of anticancer agents being underdosed is higher in the Fujimoto formula compared to the DuBois formula. In this age of international collaboration there is a need for a universal cancer treatment. It is therefore necessary to standardize the BSA formula to avoid the complexity of using multiple formulae. We recommend the DuBois formula as the standard BSA formula to calculate the dose of anticancer agents in Japan.

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